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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,443	09/02/2004	Ugur Sahin	16034US01	1542

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EXAMINER	
HALVORSON, MARK	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,443	SAHIN ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *118-134* is/are pending in the application.

4a) Of the above claim(s) *126- 134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *118-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence search results*.

DETAILED ACTION

Claims 118-134 are pending.

Election/Restrictions

Applicant's election with traverse of Group 5 in the reply filed on 4/4/2007 is acknowledged. Applicant's election with traverse of species, tumor antigen, in the reply filed on 4/4/2007 is acknowledged. The traversal is on the ground(s) that a single search can be performed that would encompass the sequence of all of the splice variants. Applicants further argue that searching the nucleic acid along with the tumor antigen would not be a search burden. This is not found persuasive because each sequence presents a structurally and functionally distinct invention not a species. Applicants point out that the peptides of SEQ ID NOs:22-24 and 58-61 are alternative splice variants and state that there would not be a search burden to search all 7 peptides. However, the sequence identity between the peptides of SEQ ID NOs:22-24 and 58-61 are sufficiently distinct to warrant separate sequence searches and searching all 7 sequences would entail a serious search burden.

In addition, the nucleic acid of SEQ ID NO:19 is related to the protein of SEQ ID NO:22 by virtue of the fact that the DNA codes for the protein. The DNA molecule has utility for the recombinant production of the protein in a host cell. Although the DNA and the protein are related, since the DNA encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by other and materially distinct processes, such as purification from the natural source. Further, DNA can be used for processes other than the production of protein, such as nucleic acid hybridization assays.

The search of the polypeptide and polynucleotide are not coextensive. The polypeptide and polynucleotide have a separate status in the art as shown by their different classifications. In cases such as this one where descriptive sequence information is provided, the sequences are searched in appropriate database. There is

search burden also in the non-patent literature. Prior to the concomitant isolation and expression of the sequences of interest there may be journal articles devoted solely to polypeptide which would not have described the polynucleotide. Similarly, there may have been "classical" genetics papers which had no knowledge of the polypeptide but spoke to the gene. Searching, therefore is not coextensive. In addition, the claims include seven distinct polypeptide sequences inclusive of various complements and fragments. This search requires an extensive analysis of the art retrieved in a sequence search and will require an in-depth analysis of technical literature. As such, it would be burdensome to search the inventions of the nucleic acid and the tumor antigen.

The restriction is still deemed proper and is therefore made FINAL.

Claims 126-134 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 118-125 are under examination.

Specification

The specification is objected to for not providing section headings.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The Specification is missing the section headings "Background of the Invention" and "Brief Summary of the Invention" and "Brief Descriptions of the Figures" headings. Further, the "Brief Descriptions of the Figures" section should be placed before the "Detailed Description of the Invention" section.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 118-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "hybridizes to" is indefinite because it is not clear as to the property boundary encompassed by the term. To overcome this

rejection the conditions for the hybridization, including the wash step, must be incorporated into claim 118, provided written support for such an amendment exists. In addition, claim 118 (iii) says that the polypeptide is encoded by antisense (i.e. nucleic acid molecule that hybridizes to the sense nucleic acid (SEQ ID NO: 19), which encodes a polypeptide. Amending the claim to "the full complementary to the nucleic acid of SEQ ID NO: 19" would obviate this part of rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 118-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of diagnosing a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises detection of the tumor-associated antigen in a biological sample isolated from a patient, wherein the tumor associated antigen is selected from the group consisting of a polypeptide of SEQ ID NO:22 or a portion thereof, a polypeptide encoded by the nucleic acid or a portion thereof and a polypeptide encoded by a nucleic acid that hybridizes to the complementary of the nucleic acid of SEQ ID NO:19 or a portion thereof.

The specification discloses that the expression of the nucleic acid of SEQ ID NO:19 is upregulated in over 30% of melanomas, prostate carcinomas, and bronchial carcinomas. (Table 2). The specification also discloses that the expression of the

nucleic acid of SEQ ID NO:19, that encodes the peptide of SEQ ID NO:22, is not upregulated or upregulated in less than 30% of patient samples in mammary carcinomas, colorectal tumors, kidney cell carcinomas, ovarian carcinomas thyroid carcinomas and cervical carcinomas. (Id).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide examples or guidance for diagnosing a disease characterized by expression or abnormal expression of the peptide of SEQ ID NO:22 comprising detecting the peptide from a biological sample isolated from a patient wherein detection of the peptide in the sample in an amount greater than that of a normal biological sample indicates the disease. The specification only demonstrates that the RNA encoding the peptide of SEQ ID NO:22 is upregulated in 30% of the patients tested for three types of cancer. There is no examples demonstrating the peptide of SEQ ID NO:22 is upregulated in any cancer. The specification does not provide a nexus between the disease status of the patient and the expression of the peptide of SEQ ID NO:22.

Chen et al (Hum Genet, 1999, 105:399-409) disclose a phosphatase, transmembrane phosphatase with tensin homology (TPTE), with an amino acid sequence identical to that of SEQ ID NO:22 of the present application. (see sequence search). TPTE mRNA was found to be expressed primarily in the testis. (Fig. 3). Tapparel et al (Gene, 2003, 189-199) found that TPTE protein was expressed in secondary spermatocytes and/or early spermatides. (page 192, 1st column). An analysis of TPTE mRNA revealed that no sequence alterations in the coding sequence of TPTE in testis cancer tissue. (page 194, 1st column). Immunohistochemical analysis on tumor tissue demonstrated low protein expression of TPTE. (Id).

Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders and associated markers such as CIN and HLA alleles and HPV type. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against

acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

Furthermore, it is well known and recognized in the art that mRNA detection is not an indication of protein production level. In particular, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, col 2) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, col 2) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into

protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page col 2) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Therefore, in view of the lack of guidance in the specification, the absence of working examples of detecting the claimed peptide, and the state of the art it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim 125 is drawn to a method of diagnosing a disease characterized by expression or abnormal expression of a tumor-associated antigen in which the tumor-associated antigen to be detected is in a complex with an MHC molecule.

The specification does not provide any examples of any peptides that are complexed with an MHC molecule and induce an immune response.

Roitt et al (Immunology, Fourth Edition, 1996, Mosby, page 7.9-7.11) teach that T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells. This is known as MHC restriction. Only a minority of peptide fragments from a protein antigen is able to bind particular MHC molecules. Different MHC molecules bind different sets of peptides. Roitt et al specifically teach Fig. 7.22 and Fig. 7.23, and also page 7.10, right column that the peptides sizes 12-15 are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I.

The specification provides insufficient guidance with regard to the nature of the peptide that being complexed with an MHC in a disease. The specification does not provide any working example of any peptide that would work with any MHC molecule in cancer, or any other disease. Considering the state of art, the broad scope of claims in respect to the nature of peptide and also to the nature of MHC molecules, it is

concluded that undue experimentation is required to practice the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Summary

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at (571) 272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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571-272-6539

Primary Examiner